CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761068Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761068
PDUFA Goal Date	April 17, 2018
OSE RCM #	2017-1716 & 2017-1718
Reviewer Name	Mona Patel, PharmD, RAC, Division of Risk Management (DRISK)
Team Leader	Leah Hart, PharmD, DRISK
Deputy Director	Jamie Wilkins Parker, PharmD, DRISK
Review Completion Date	March 22, 2018
Subject	Evaluation of Need for a REMS
Established Name	burosumab
Trade Name	Crysvita
Name of Applicant	Ultragenyx Pharmaceutical, Inc.
Therapeutic Class	fibroblast growth factor 23 inhibitor
Formulation	solution
Dosing Regimen	1 mg/kg body weight up to a maximum dose of 90 mg every four weeks

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Executive Summary

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Crysvita (burosumab) is necessary to ensure the benefits of this product outweigh its risks. Ultragenyx Pharmaceutical, Inc submitted a Biologics Licensing Application (BLA 761068) for burosumab with the proposed indication of the treatment of adult and pediatric patients 1 year of age and older with X-linked hypophosphatemia (XLH). The risks associated with the use of burosumab include injection site and hypersensitivity reactions (e.g. rash, urticaria), and hyperphosphatemia with potential risk for nephrocalcinosis. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Bone, Reproductive and Urologic Products (DBRUP) agree that a REMS is not necessary to ensure the benefits of burosumab outweigh its risks. Burosumab has proven to reduce the severity of symptoms in patients with XLH. Based on the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required. In general, healthcare providers who treat XLH should be familiar with the risk associated with burosumabdue to the adverse event profile of conventional therapies used to treat X-linked hypophosphatemia.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Crysvita (burosumab) is necessary to ensure the benefits of this product outweigh its risks. Ultragenyx Pharmaceutical, Inc. submitted a Biologics Licensing Application (BLA 761068) for burosumab on August 17, 2017, for the proposed indication of the treatment of adult and pediatric patients 1 year of age and older with X-linked hypophosphatemia (XLH). This application is under review in the Division of Bone, Reproductive and Urologic Products (DBRUP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Burosumab, a new molecular entity,[a] is a fully human monoclonal antibody (mAb) that binds to fibroblast growth factor 23 (FGF23), which is responsible for phosphate and vitamin D metabolism, and inhibits FGF23 biologic activity that is responsible for the pathophysiology of XLH. Burosumab inhibits the excess production of FGF23 triggered by the inactivating mutations of the phosphate-regulating gene with homologies to endopeptidases on the X chromosome caused by XLH. Burosumab is proposed for the treatment of adult and pediatric patients 1 year of age and older with X-linked hypophosphatemia (XLH).

Burosumab is proposed to be available as 10 mg/mL, 20 mg/mL, or 30 mg/mL solution in a single-use vial to be administered via subcutaneous injection in adult patients (age ≥18 - 65 years) at 1 mg/kg body

[a] FDAAA factor (F): Whether the drug is a new molecular entity

weight up to a maximum dose of 90 mg every four weeks.[b] For pediatric patients (age 1 to <18 years old), the starting dose is 0.8 mg/kg body weight every two weeks. In pediatric patients, the dose may be increased up to 2 mg/kg every two weeks to achieve normal serum phosphorus. For both patient populations, the dose is to be rounded to the nearest 10 mg. It may be administered by a healthcare professional (b) (4)

Burosumab was designated as an orphan drug for the treatment of XLH on December 14, 2009, and was granted fast track designation on June 30, 2015 for the treatment of XLH and breakthrough therapy designation on June 22, 2016. The Biologics Licensing Application (BLA 761068) for burosumab received priority review classification on October 3, 2017.

Burosumab has never been approved in the U.S. In Dec. 2017, the scientific committee of the European Medicines Agency (EMA) recommended granting conditional marketing authorization for the treatment of XLH with radiographic bone disease in children age ≥1 year of age and adolescents with growing skeletons.[1]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761068 relevant to this review:

- 6/30/2015: Fast Track designation granted (IND 76488)
- 6/22/2016: Breakthrough Therapy designation granted
- 6/19/2017: A preliminary discussion on the need for a REMS was held at the pre-BLA meeting. The Agency informed the Applicant that the division had insufficient information to determine whether a REMS would be necessary and that the determination for a REMS would occur during the review of the application.
- 7/11/2017: Rare Pediatric Disease Designation granted
- 8/17/2017: BLA 761068 submission for burosumab injection to treat adult and pediatric patients 1 year of age and older with X-linked hypophosphatemia (XLH).
- 10/3/2017: BLA 761068 received priority review classification.
- 11/30/2017: A Mid-Cycle Communication was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, a REMS will not be necessary to ensure the benefits of the drug outweigh the risks.
- 02/15/2018: A Late-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for burosumab.

3 Therapeutic Context and Treatment Options

[b] FDAAA factor (D): The expected or actual duration of treatment with the drug

3.1 DESCRIPTION OF THE MEDICAL CONDITION

X-linked hypophosphatemia (XLH) is a deformative bone disease caused by mutations in the PHEX (Phosphate-regulating Endopeptidase on the X chromosome) gene that affects an individual's day to day functioning and quality of life starting from a young age.[c] It is an orphan disease which is lifelong and debilitating. The two major pathologic consequences of XLH in the bone are osteomalacia and rickets. Rickets is a disease affecting children characterized by deficient mineralization and delayed endochondral ossification of the growth plates that lead to reduced growth and skeletal deformities including bowing of the lower extremities. Hypophosphatemia, osteomalacia, reduced height, and lower extremity deformities will typically persist through adulthood. Adults with XLH will experience significant morbidity due to years of chronic hypophosphatemia and develop early osteoarthritis . It is estimated that 12-16,000 patients are living with XLH in the United States and the incidence rate for XLH globally is estimated to be 1 in 20,000 live births.[d,2]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are no approved treatments for XLH. For adults and children, current therapy for XLH consists of oral administration of phosphate to replace renal losses and calcitriol to increase the intestinal absorption of calcium, prevent secondary hyperparathyroidism, and to suppress PTH release directly. The general goal of therapy with both treatment options is to supplement the body's phosphate to allow mineralization of bone and improve skeletal outcomes and associated symptoms. Calcitriol is typically administered both in adults and children in two doses per day
(10 to 20 nanograms/kilogram per dose). For adults, phosphate is typically administered in a dose of 1 to 4 g/day in 3 to 4 divided doses. For children, phosphate is administered in 4 to 5 divided doses; the starting dose in children is 40 mg of elemental phosphorus/kg per day, and then the daily phosphorus dose can be increased in steps of 250 mg to 500 mg up to a maximum of 3500 mg/day. The amount of phosphorus supplementation is limited by the occurrence of diarrhea. If diarrhea is a problem, the dose of phosphorus should be decreased by 250 to 500 mg and then re-increased in steps of 125 mg. Since the aim of treatment in pediatrics is to achieve normal growth, therapy is maintained if the growth plates are open (usually up to the age of 15 to 17 years). Once a patient reaches adult height and the epiphyses have fused, the goal of therapy is simply to manage generalized bone pain and enhance limited mobility.

Two important complications of the current treatment options for XLH are nephrocalcinosis and hyperparathyroidism. It has been speculated that the development of nephrocalcinosis results from increases in urinary phosphate and urinary calcium (from calcitriol). Careful monitoring of serum phosphorus and calcium and dose reduction of calcitriol and/or phosphate supplementation should occur when increases in urinary phosphate and calcium occur. Hyperparathyroidism has also been

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[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

reported in XLH patients usually after years of treatment. It is thought that calcium with phosphate supplements result in intermittent hypocalcemia and persistent stimulation of parathyroid hormone (PTH) release despite the administration of calcitriol.[3,1] There is a clear unmet medical need with the lack of FDA-approved treatment options to treat XLH.

4 Benefit Assessment

Evidence of the effectiveness of burosumab for the treatment of XLH in adults was primarily derived from a double-arm phase 3 study (UX023-CL303) and a single-arm, Phase 3 study (UX023-CL304). In pediatric patients, effectiveness of burosumab for the treatment of X-linked hypophosphatemia (XLH) was primarily derived from a Phase 2 study (UX023-CL201) and an open-label study (UX023-CL205).

The phase 3 study, UX023-CL303, was a randomized, double-blind, placebo-controlled study to confirm the efficacy and safety of burosumab treatment and establish its impact on functional outcomes and patient reported outcomes (PROs) including skeletal pain, fatigue, stiffness, and motor function in adults with XLH. Burosumab was administered at 1 mg/kg of drug or placebo subcutaneously (SC) every 4 weeks for 24 weeks. Subjects randomized to the placebo group were then crossed over to burosumab treatment at Week 24. All subjects continued burosumab treatment for an additional 24 weeks in a Treatment Continuation Period and then continued treatment for an additional 48 weeks in a Treatment Extension Period (until Week 96). The primary efficacy endpoint was the proportion of subjects achieving mean serum phosphorus levels above the lower limit of normal (2.5 mg/dL) at the midpoint of the dose interval (i.e., 2 weeks after each dose of the study drug, the time of peak pharmacodynamic effect) as averaged across dose cycles between baseline and Week 24. The primary analysis of the phosphorus response endpoint was conducted using the Cochran-Mantel-Haenszel test adjusted for the randomization stratification factors and was tested at a 2-sided level of significance ($p<0.05$). Key secondary efficacy endpoints assessed changes in subject reports of pain at its worst ($p<0.05$). The primary analysis of the secondary endpoint of pain was measured with the short-form brief pain inventory (BPI) questionnaire.

One hundred thirty-four subjects were enrolled. One hundred and thirty-three patients completed the 48 weeks of treatment and then transitioned into the extension phase. During the initial 24 weeks of treatment, the mean serum phosphorus across the midpoint of dose intervals was 2.08 mg/dL and 3.24 mg/dL in the placebo and burosumab groups respectively, and mean serum phosphorus across the ends of dose intervals was 2.05 mg/dL and 2.72 mg/dL in the placebo and burosumab groups respectively which resulted in a total of 94.1% of subjects in the burosumab group achieving a mean serum phosphorus concentration above the lower limit of normal (LLN) (2.5 mg/dL) across the midpoints of the dose intervals through Week 24 compared with only 7.6% of subjects in the placebo group ($p < 0.0001$).[1] Based on the clinical reviewer assessment, the results of the primary endpoint were clinically and statistically significant whereas for the secondary endpoint of pain, the scores on the BPI were not statistically significant ($p=0.0919$). The BPI ranged from 0 (no pain) -10 (worse possible pain). Mean (SD) baseline worst pain score was 6.54 (1.433) in the placebo group and 6.81 (1.308) in the burosumab

group. After 24 weeks of treatment, mean worst pain scores declined to 6.09 in the placebo group and 5.82 in the burosumab group. [e14]

The companion phase 3 study, UX023-CL304, was an open-label, single-arm study in adult patients to assess the effects of burosumab on improvement of osteomalacia. Burosumab was administered 1.0 mg/kg subcutaneously every 4 weeks for 48 weeks. The primary efficacy endpoint was the percent change from baseline in osteoid volume (OV/BV).

Fourteen patients were enrolled and all completed 48 weeks on study. After the treatment period, healing of osteomalacia was observed in 2 patients as demonstrated by decreases in OV/BV from 24.3 and 28.5 to 8.6 and 7.4 respectively.[4] Based on the clinical reviewer assessment, the results of the primary endpoint were determined to be clinically significant.

In pediatric patients, the phase 2 study, UX023-CL201, is an ongoing, randomized, open-label study designed as a dose-finding study to determine whether every 2 weeks or every 4 weeks dosing of burosumab provides the optimal profile of phosphate control and clinical efficacy. The burosumab dose is adjusted to target a fasting serum phosphorus concentration of 3.5 to 5.0 mg/dL. Following an initial 16-week dose titration phase, patients completed 48-weeks of treatment and then entered a single arm 96-week extension phase with burosumab every 2 weeks. The primary efficacy endpoint is change from baseline of mean serum phosphorus levels and clinical outcomes and manifestations of XLH, including rickets, growth, physical function, and patient-reported outcomes such as pain and functional disability. The primary analysis of the healing was conducted using the Thacher Rickets Severity Score (RSS) and the 7-point Radiographic Global Impression of Change (RGI-C).

At the time of the 120 Day Safety update, fifty-two patients were enrolled and all completed at least 64 weeks on study. Mean serum phosphorus levels increased from 2.38 at baseline to 3.30 and 3.35 mg/dL at week 40 and week 64 in patients who received burosumab every 2 weeks. After 40 weeks of treatment with burosumab, mean total RSS improved significantly in all 52 patients from 1.92 to 0.75 in patients receiving burosumab every two weeks. After 40 weeks of treatment, the mean RGI-C Global score was 1.66 in patients receiving burosumab every two weeks ($p < 0.0001$) demonstrating healing of rickets. As for growth, one of the primary endpoints, in all 52 patients, burosumab treatment for 40 weeks increased standing mean (SD) height Z score from -1.72 at baseline to -1.54 in the patients who received burosumab every 2 weeks.[4] Based on the clinical reviewer assessment, the results of the primary endpoint were determined to be clinically and statistically significant.

The phase 2 study, UX023-CL205, is an ongoing open-label, single-arm study in pediatric patients age 1-4 y/o to establish the safety profile of burosumab and determine the effects of pharmacodynamic markers of phosphate homeostasis in this age group. Burosumab is administered at a starting dose of 0.8 mg/kg every 2 weeks (Q2W) with one dose adjustment to 1.2 mg/kg Q2W allowed if serum phosphorus increases by <0.5 mg/dL from baseline and two consecutive measures are below lower limit of normal. The duration of treatment is for 64 weeks. The primary efficacy endpoint is change from

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

baseline of serum phosphorus levels and clinical outcomes and manifestations of XLH, including rickets, growth, physical function, and patient-reported outcomes such as pain and functional disability.

At the time of the 120 Day Safety update, thirteen patients were enrolled and all completed at least 30 weeks on study. Mean serum phosphorus levels increased from 2.51 mg/dL at baseline to 3.47 mg/dL at week 40. After 40 weeks of treatment with burosumab, mean total RSS improved significantly in all 52 patients from 2.92 to 1.19 in patients receiving burosumab every two weeks. After 40 weeks of treatment, the mean RGI-C Global score was 2.33 in patients receiving burosumab every two weeks ($p < 0.0001$) demonstrating healing of rickets.[4] Based on the clinical reviewer assessment, the results of the primary endpoint were determined to be clinically and statistically significant.

5 Risk Assessment & Safe-Use Conditions

The total safety population was 241 patients comprised of 176 adults and 65 pediatric patients. Safety data in adults was primarily derived from a phase 3 study (UX023-CL303), and in pediatric patients the safety of burosumab was primarily derived from the phase 2 study (UX023-CL201) and (UX023-CL205). In adults, a total of 68 subjects with XLH received burosumab at 1mg/kg in the clinical trial. Common AEs that occurred at a rate of at least 5% and at a higher rate in the burosumab group than in the placebo group during the 24-week placebo-controlled period included back pain, headache, tooth infection, restless legs syndrome, Vitamin D decrease, dizziness, constipation, and blood phosphorus increase.[4] Grade 3 treatment emergent adverse events (TEAEs) were reported for 8 (12%) subjects in the burosumab group and 9 (14%) subjects in the placebo group; no Grade 4 TEAEs were reported. Back pain (15%, 9%); tooth abscess (13%, 8%); headache (13%, 8%); restless legs syndrome (12%, 6%); and nasopharyngitis (13%, 9%) were the most frequently reported TEAEs.[1] None of the 68 adult patients discontinued drug due to an adverse event.

In pediatric patients, a total of 65 patients with XLH received burosumab that included 52 exposed for at least 64 weeks (Study 201) and 13 exposed for at least 24 weeks (Study 205). Common adverse events (AEs) that occurred at a rate of at least 10% and at a higher rate in the burosumab group than in the placebo group in Study 201 and 205 include injection site reaction, headache, pain in extremity, vitamin D decrease, rash, toothache, myalgia, tooth abscess, and dizziness.[4] All pediatric patients experienced at least one TEAE. Injection site reactions were the most frequent category of AEs. None of the 65 pediatric patients discontinued drug due to an adverse event.

Two SAEs, in terms of frequency, injection site and hypersensitivity reactions, were generally mild in severity (Grade 1) for adults and pediatric patients. None resulted in drug discontinuation and nearly all resolved without treatment.

There were no deaths in any of the XLH studies, pediatric or adult, through the data cutoffs for the 120-day safety update. The pregnancy data submitted in the 120 Day Safety Update during clinical trials of burosumab did not inform a drug-associated risk of adverse developmental outcomes. Analysis of expected adverse reactions did not identify a safety signal that would warrant a REMS.

5.1 Adverse Event of Special Interest

The most significant SAE in burosumab treated subjects for both adults and pediatric patients was hyperphosphatemia with a potential risk of nephrocalcinosis.

5.1.1 Hyperphosphatemia & Risk of Nephrocalcinosis

In the adult study, the normal range for serum phosphorus was designated as 2.5-4.5 mg/dL which is the upper limit of normal (ULN) in adults. In the adult study, 9 patients treated with burosumab had at least one level above 4.5 mg/dL and 5 of these patients had dose reductions due to hyperphosphatemia. In the placebo group, no patient had high serum phosphorus during the double-blind period. In the pediatric studies, the normal range for serum phosphorus was designated as 3.2-6.1 mg/dL which is below the ULN for pediatric patients. In the pediatric studies, 6 patients treated with burosumab had at least one level above 4.5 mg/dL and 3 of these patients had dose reductions due to hyperphosphatemia. There were no discontinuations of drug in either arm of the study.

In general, hyperphosphatemia is a risk factor for nephrocalcinosis which is a term used to describe deposition of calcium salts in the renal parenchyma due to hyperparathyroidism.[1] In study CL201, nephrocalcinosis scores were unchanged from baseline in 36/52 patients (69%); decreased by 1 point in 3/52 patients (6%)(improved); and increased by 1 point in 13/52 patients (25%)(worsened). In study CL303 as well, small increases (1 point) in nephrocalcinosis scores were more frequent than 1-point score decreases, however burosumab and placebo groups were similar in this regard. There were no score increases >1 point in these studies, and the 1-point increases were not associated with increased urinary calcium or decreased renal function.[1]

Although the risk of nephrocalcinosis with burosumab appears to be low, it will be recommended in labeling that all patients treated with burosumab undergo monitoring of serum phosphorus, at least during the first 3 months of treatment and following any change in dose. As there are some uncertainties about the potential for nephrocalcinosis and/or renal impairment with long term use, the Applicant will be required to conduct a postmarketing requirement to collect data for 10 years to evaluate whether there is an association between treatment with burosumab and the occurrence of nephrocalcinosis and renal failure.

6 Expected Postmarket Use

The likely prescribers will be endocrinologists who should be familiar with the risk of hyperphosphatemia with a risk factor for nephrocalcinosis due to the adverse event profile of conventional therapies used to treat X-linked hypophosphatemia. Burosumab may be administered by a healthcare professional (b) (4) . As there are some uncertainties about the potential for nephrocalcinosis and/or renal impairment with long term use, the Applicant will be required to conduct a postmarketing requirement to collect data for 10 years to evaluate whether there is an association between treatment with burosumab and the occurrence of nephrocalcinosis and renal failure.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for burosumab beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of burosumab based on the efficacy and safety information currently available.

The efficacy data for burosumab supports approval for the treatment of adult and pediatric patients 1 year of age and older with X-linked hypophosphatemia (XLH). In studies of adults with XLH, burosumab was associated with clinically and statistically significant increases in serum phosphorus and improvements in osteomalacia, as shown by decreases is osteoid volume/bone volume compared to placebo. A total of 94.1% of patients treated with burosumab achieved a serum phosphorus level above the lower limit of normal compared to 7.6% in the placebo group through week 24.

In studies of children with XLH age 1-12 years of age, burosumab was associated with clinically and statistically significant increases in serum phosphorus, and significant improvement in radiographic rickets scores and serum alkaline phosphatase. Mean serum phosphorus levels increased from 2.38 to 3.30 and 3.35 mg/dL at week 40 and week 64 in patients who received burosumab every 2 weeks. After 40 weeks of treatment with burosumab, mean total RSS improved significantly in all 52 patients from 1.92 to 0.75 in patients receiving burosumab every two weeks. After 40 weeks of treatment, the mean RGI-C Global score was 1.66 in patients receiving burosumab every two weeks ($p < 0.0001$) demonstrating healing of rickets. These changes are expected to result in substantial improvements in long-term clinical outcomes of growth and skeletal deformities.

Analysis of the SAEs did not identify a safety signal that would warrant a REMS, and there are no drugs currently approved with a similar safety profile that have a REMS. Overall, the injection site and hypersensitivity reactions were generally mild in severity (Grade 1) for adults and pediatric patients. None resulted in drug discontinuation and nearly all resolved without treatment. As for the cases of hyperphosphatemia, withholding the next dose and re-assessing serum phosphorus levels in 4 weeks with re-initiation of treatment according to a dose schedule resolvedall cases. The cases resulting in small increases in nephrocalcinosis scores were not associated with increased urinary calcium or decreased renal function. Although the risk of nephrocalcinosis with burosumab appears to be low, it will be recommended that all patients treated with burosumab undergo monitoring of serum phosphorus, at least during the first 3 months of treatment and following any change in dose. As there are some uncertainties about the potential for nephrocalcinosis and/or renal impairment with long term use, the Applicant will be required to conduct a postmarketing requirement to collect data for 10 years to evaluate whether there is an association between treatment with burosumab and the occurrence of nephrocalcinosis and renal failure. These SAEs will be communicated through labeling in the Warnings & Precautions section.

The likely prescribers will be endocrinologists who should be familiar with the risk of hyperphosphatemia with a risk factor for nephrocalcinosis due to the adverse event profile of conventional therapies used to treat X-linked hypophosphatemia.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with burosumab will be addressed in labeling, and in general, healthcare providers who treat X-linked hypophosphatemia should be familiar with the risk of hyperphosphatemia with a risk factor for nephrocalcinosis due to the adverse event profile of conventional therapies used to treat X-linked hypophosphatemia.

Should DBRUP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES

1. Voss, Stephen. Unireview for Crysvita (burosumab), BLA 761068, February 9, 2018

2. Rafaelsen, SH, Johansson, S, Raeder, H, and Bjerknes, R. 2016. “Hereditary hypophosphatemia in Norway; a retrospective population-based study of genotypes, phenotypes and treatment complications.” European Journal of Endocrinology 174 (2): 125-36.

3. Carpenter TO, Mitnick MA, Ellison A, Smith C, Insogna KL. “Nocturnal hyperparathyroidism: a frequent feature of X-linked hypophosphatemia.” J Clin Endocrinol Metab. 1994;78(6):1378.

4. Crysvita (burosumab) US Prescribing Information (January 17, 2018)

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/s/

MONA G PATEL
03/22/2018

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03/22/2018